

## Ethical Decisions in the History of Organ Transplantation

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**D**R. THOMAS, DR. JONES, members, and guests of The Southern Surgical Association. A year ago in Boca Raton, when elected President of this Association, I was literally speechless and, as I recall, my comments were brief and certainly not appropriate for the occasion. During the past 12 months, I have had ample time to think about the magnitude of the honor and to prepare for the 101st meeting of The Southern. The following thoughts will be better organized and more accurately reflect my feelings.

To be elected President of The Southern Surgical Association is truly an enormous honor, one that will never be forgotten and, in one way or another, has remained somewhere in my cortex available for review nearly every day of the past year. It is only appropriate for me to accept this honor as a recognition of all the members of this Association who are surgeons in the state of Alabama and the faculty and house staff of the Department of Surgery of The University of Alabama School of Medicine. For me to say thank you would be inadequate, and I hope that my gratitude will be reflected through my professional activities in the years to come.

The kind remarks of introduction by Dr. Thomas are only partly true, and at this moment I'm unsure of where the facts end and the fiction begins.

It is not difficult for me to determine the point at which I became interested in the field of surgery. It occurred in my third year of medical school and was largely due to the contact with Dr. Frank Glenn, Professor and Chairman of the Department of Surgery at the Cornell Medical College and Surgeon in Chief of the New York Hospital. Dr. Glenn, a member of this Association from 1947 until his death in 1983, was a frequent contributor to the scientific sessions. In December of 1961, as a resident, I at-

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tended my first meeting of The Southern as a coauthor of a paper with Dr. Glenn concerning constrictive pericarditis. I remember that meeting held at The Homestead very well, and it is difficult to believe that 28 years later I stand before you about to deliver the Presidential address.

There are many people to whom I owe much gratitude regarding my professional life. In addition to Dr. Glenn, I would like to mention them briefly at this time. Dr. Joseph Murray, Professor of Surgery at Harvard Medical School and the Peter Bent Brigham Hospital, and Dr. Francis Moore, Mosely Professor of Surgery and Surgeon in Chief at the Brigham, provided stimulation and support at a time when both were needed. It was at the Brigham that I received my introduction to the field of transplantation, which provided the foundation for my academic future. The 2 years of clinical and research experience with Dr. Moore and Dr. Murray instilled in me many of the important principals of surgical research. At a later time I had the good fortune to spend 6 months with Sir Peter Medawar and Dr. Eugene Lance at Northwick Park Hospital in England. Time doesn't permit me to elaborate on this experience; however the frequent luncheons with Sir Peter and his staff remain fond memories. In 1967 it was my good luck to be offered a position as Assistant Professor of Surgery at The University of Alabama by Dr. John W. Kirklin, the Chairman of the Department and a former member of this Association. Little did I realize that it would be my last academic move and eventually allow me the opportunity to succeed Dr. Kirklin as the Chairman of that Department. Nor did it occur to me in 1967 that under his leadership surgery would become a major department in a medical school and hospital that would enjoy more than 20 years of growth and prosperity far exceeding the expectations of the most optimistic

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members of the faculty. John Kirklin has had an outstanding career as a cardiac surgeon, and his contributions as Chairman of the Department of Surgery to the development of the Medical School are equally great. His leadership combined the academic and the clinical practice of surgery to create a sound and unique format that will maintain a successful foundation for many years to come.

### **Ethical Decisions in the History of Organ Transplantation**

I would now like to discuss with you a subject of importance to medicine, surgery, and, in particular, organ transplantation, which extends from the early 1950s to the present and will continue to be of interest and relevance in the years to come. That subject concerns some of the ethical problems confronting organ transplantation. Ethics is defined by Webster's *New World Dictionary* (Second College Edition published in 1970) 'as the study of standards of conduct and moral judgement.' Webster also defines moral 'as relating to, dealing with, or capable of making the distinction between right and wrong in conduct.' As the science of medicine advances, many of the ethical problems confronting physicians, surgeons, and society change and thus require careful scrutiny. Some ethical problems have been solved by scientific progress while others persist because medicine has not yet provided a solution or because society is unwilling to accept the proposed solution. Organ transplantation is the process whereby diseased organs are replaced by other organs or possibly individual cells as a means to restore normal physiologic function. Most, if not all, of the ethical problems confronting the field of transplantation relate to the need for human organs and their procurement. The presentation this morning will deal with these problems.

#### *Human Experimentation*

Ethical decisions in the history of medicine have existed for centuries and are not unique to our time. However as times change so do the governments of nations, the practice of medicine, and patient care needs. The changes in medical practice have increased in tempo since the turn of this century and especially in the last 40 years. These changes in medicine, coupled with the relationship of the federal government to providing partial or complete financial coverage of the patient, require special thought regarding the application of new forms of medical treatment. Thus medical care today is both a social and economic problem and, as such, pertains to those ethical concerns involving the available resources required for providing medical care.

Medical ethics applied to organ transplantation involves two specific areas. The first is the subject of human experimentation—a broad issue pertaining to medicine as

a whole. The second is the shortage of available organs required for patients awaiting transplantation. It is the organ shortage that presents the most important immediate obstacle for clinical transplantation and will become worse in the foreseeable future.

Human experimentation as it pertains to organ transplantation has been discussed<sup>1-10</sup> since the first living related donor transplant operation reported by Merrill and Murray in 1956.<sup>9</sup> However the use of human subjects in medical experiments predates the first living related donor transplant. In 1948 Ivy<sup>11</sup> summarized the history and ethics of using human subjects in medical practice. He noted that when Harvey, in 1628, described the existence of circulation in humans he also reported controlled observations in animals. Harvey is said to have demonstrated to King Charles I that the accidental exposure of the heart from the outside allowed the observation that the heart could be touched without pain. In 1798 Jenner published experimental human data on vaccination against smallpox. Other examples included the testing of chloroform and ether on physicians, as well as other experiments, some of which led to misadventure. Ivy proceeded to discuss the use of prisoners, mental incompetents, and medical and lay subjects as human volunteers. The Nuremberg code for permissible human experimentation was an outgrowth of the war crimes occurring in World War II against German defendants held accountable for experiments involving human subjects.<sup>1</sup> Ten standards were identified to which physicians had to adhere if experimentation on human subjects was to occur. This was followed by a code of ethics of the World Medical Association as proposed by the Declaration of Helsinki in 1964, which described voluntary consent as absolutely essential.<sup>1</sup> Informed or voluntary consent, necessary for the preparation of patients for operation, has been particularly important in the selection of the donor for living related transplantation. Beecher,<sup>1</sup> in 1959, reviewed the status of experimentation in humans and in 1966 addressed the subject, emphasizing that 'consent is not the physician's for the asking'.<sup>2</sup> He reviewed the ethical, sociologic, and legal implications involved in informed consent and stated that 'a study does not become ethical merely because it turns up valuable data'. Moore,<sup>12</sup> in 1968, stated that 'good biomedical science has an ethic that appeals to the humanist' and 'the same factors which make new operations scientifically acceptable are those that make them ethically acceptable' (Fig. 1). Twenty-one years later Moore again examined ethical considerations involving patients undergoing new transplantation procedures and described the 'desperate remedy phenomenon' in which patients are so ill that 'almost anything was welcomed by the patient, the family and the physicians'.<sup>15</sup> Scientific progress is the solution to the 'desperate remedy phenomenon' and can change this 'phenomenon' by performing care-



FIG. 1. Dr. Francis D. Moore, former Professor of Surgery at Harvard Medical School and Chairman of the Department of Surgery at the Peter Bent Brigham Hospital, was a major stimulus behind experimental and clinical renal transplantation. The importance of research—clinical and laboratory—in the quest for new knowledge, combined with compassionate care for the patient, led him to the following statement published in *JAMA* in 1968, 'The same factors which make new operations scientifically acceptable are those that make them ethically acceptable.'

fully designed research studies involving animal experimentation as a prelude to clinical trials.

To place new and untried procedures in proper perspective, Moore<sup>13</sup> proposed three fundamental principles, (1) a scientific research background on which the procedure is based, (2) the skill of the surgeons or physicians, and (3) the ethics of the institution. Unfortunately some institutions have entered the field of transplantation without numbers one and three and have used the surgeon's skill as their explanation for their need to develop a transplant center. To develop a transplant program to compete with a nearby hospital without the proper scientific support is more likely an attempt by the institution to generate new revenue and public attention rather than new knowledge.

#### *The Living Donor and the Organ Shortage*

The common thread of most ethical decisions involving organ and tissue transplantation from the first successful

kidney transplant in 1954 to the present pertains to (1) informed voluntary consent in the donor, the very basis of human experimentation; and (2) the shortage of organs. Many of the complex ethical questions regarding the shortage of organs for transplantation would be avoided if organs could be constructed and purchased as one does a vascular graft, a prosthetic aortic valve, a cardiac pacemaker, and so on. However, because organs cannot be made, they must be donated from humans—living or dead—and therein lies the problem. The demand for replacement of diseased organs (*i.e.*, heart, lung, liver, kidney, and pancreas) and functioning cells (*i.e.*, pancreatic islet cells) is so great and the current available supply so limited that solutions to resolve this need have, in turn, created important ethical and medical questions. With these comments in mind, one can pursue the subject in a chronologic manner, beginning with the early 1950s.

#### **Possible Solutions to Organ Shortage**

##### *The Living Related Donor*

The early unsuccessful efforts of clinical renal transplantation using cadaveric organs were reported by Hume in 1955<sup>14</sup> (Fig. 2). These results were not surprising considering the use of organs from non-heartbeating cadavers, the absence of organ preservation, and the inadequate immunosuppressive drugs available at that time for prevention and treatment of allograft rejection. Because cadaveric renal transplantation was unsuccessful and the proved observation that identical twins would not reject tissue from one another, it was recognized that renal transplantation might be feasible if carried out between identical twins, assuming that one twin had irreversible renal failure and the other was a healthy and willing donor. Fundamental to this operation was the knowledge that a renal autograft performed in dogs would function normally and denervation of the kidney produced no apparent physiologic dysfunction.<sup>15</sup>

On December 23, 1954, 3 weeks after the 66th Annual Meeting of The Southern Surgical Association at The Hollywood Beach Hotel in Hollywood, Florida, Dr. Joseph Murray (Fig. 3) and colleagues performed a living related donor kidney transplant between two brothers at the Peter Bent Brigham Hospital<sup>9,16</sup> (Fig. 4). Because the two were identical twins, graft rejection did not occur. The transplanted kidney functioned immediately and both brothers were discharged well and in good health some weeks later (Fig. 5). This was a momentous operation because, for the first time, renal transplantation was used as a successful means of replacing diseased organs with new ones (Fig. 6). Even though the transplant operation was successful, the immediate clinical impact was minimal because of the obvious limitation of requiring individuals with chronic renal failure to be so fortunate



FIG. 2. Dr. David M. Hume, Professor and Chairman of Surgery at the Medical College of Virginia, was a leader in renal transplantation from 1947 until his death in 1973. He pioneered the early clinical experience in cadaveric transplantation and living related donor transplantation. Tissue typing, organ procurement, and organ sharing were among his interests long before they were used by others.

to have an identical twin. The notion, however, that diseased organs could be replaced with new ones caught the imagination of the surgical world and was the driving force behind the then-new and rapidly growing field of organ and tissue transplantation. One might reflect at this moment on the clinical and ethical decisions confronting Dr. Murray and colleagues regarding the removal of a kidney from a living patient for transfer to an ill relative. First the operative and perioperative mortality and morbidity to the donor had to be considered, as well as the long-term risks and imponderables involved for a person living with one kidney. The donor and recipient, completely informed of these considerations, agreed to proceed with the operation and thus set the stage for subsequent similar transplant procedures. This serious decision was the first of many complex questions to be confronted by patients and their donors. For example, what was the life expectancy for a healthy person with one kidney after donating

the other? The best information at that time came from insurance companies, which indicated that the loss of one kidney in an otherwise healthy person had little effect on the longevity of that individual. Despite this comforting bit of information, physicians recognized that an obstructed ureter to a solitary kidney caused by a renal calculus would be an important medical problem. Even more so, a renal tumor or trauma in a solitary kidney requiring nephrectomy would cause the donor to become a transplant recipient. Thus 35 years later it is still impossible to define and assess all the potential risks confronting the donor patient. The request for kidney donation was more complex when the donor was less than 18 years old and parental consent was required. Considerable discussion preceded the first such operation at the Peter Bent Brigham Hospital and legal counsel concluded that as long as the patient required the operation and the donor and the parents, *i.e.*, guardians, agreed, then it was legally per-

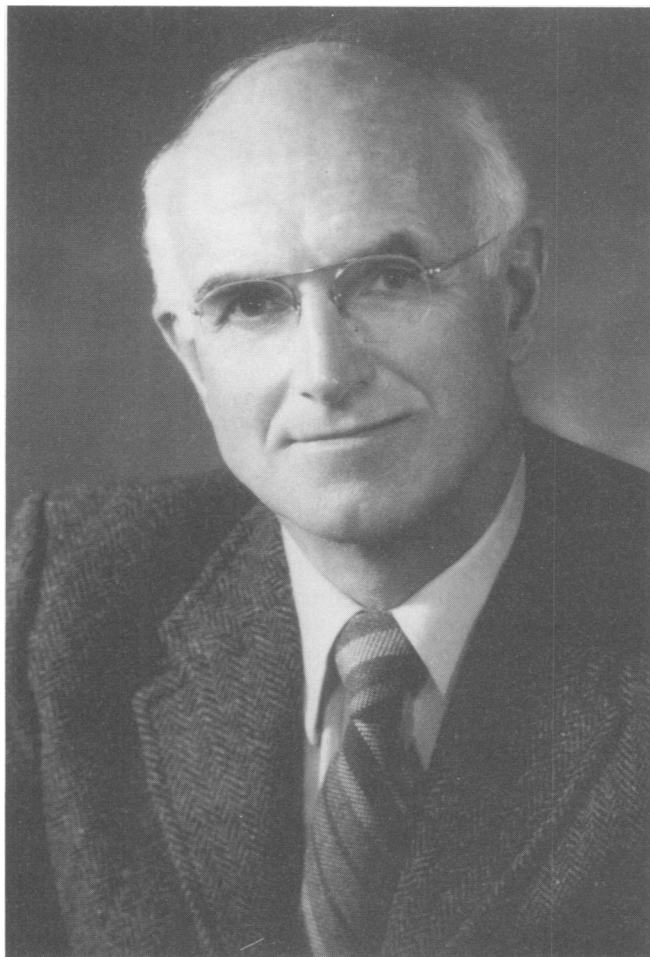


FIG. 3. Dr. Joseph E. Murray. From the first successful living donor operation in an identical twin to the beginnings of immunosuppressive therapy and the combination of multiple drugs, Dr. Murray spanned the field of renal transplantation both in the laboratory and the operating room.

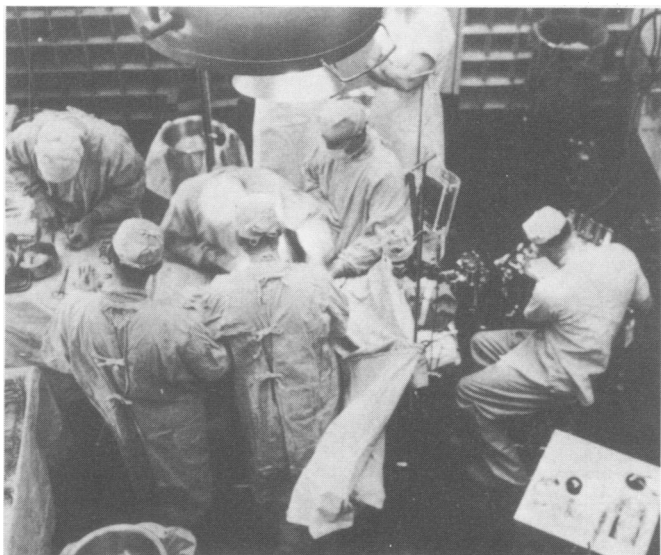


FIG. 4. Dr. Joseph E. Murray and colleagues performing the first living related donor operation in the Peter Bent Brigham Hospital in December 1954.

missible for the sibling to proceed with the kidney donation. The age limit was set at 12 to 13 years, implying that donors younger than that age would probably not have a complete grasp of the magnitude of the question and the potential risks for the future.<sup>17</sup>

#### *Informed Consent and the Living Related Donor*

The use of living donor kidneys, related or unrelated, is based on informed consent. This consent should indicate the patient's awareness of the proposed treatment, including a careful explanation by the physician to the patient. The patient, *i.e.*, donor, must (1) understand the procedure and the risks and imponderables, (2) not be coerced, (3) provide a voluntary answer, and (4) be mentally competent and of legal age. If the above cannot be provided, the individual is not an acceptable living donor.

After the first living related transplant operation performed in 1954, the procedure was used infrequently during the next 8 years, and when it was used, it was primarily in identical twins. In 1963 the drug azathioprine was introduced as a means to modify the immune response of rejection.<sup>18</sup> From this time forward renal transplantation between living related donors became more frequent with additional immunosuppressive therapy to prevent rejection. All physicians participating in organ transplantation recognize the tremendous medical and ethical responsibility that is placed on those surgeons involved in both the donor and recipient operations. The acceptance of living donor transplantation is not unanimous and, in some centers, the donor risks are considered too high and only cadaveric kidneys are used. The definition of 'too

high' remains relative. One death in 1500 operations is often used as the probable risk to the donor, but there is no collected data to support the statement. At the University of Alabama, we have carried out renal transplantation between living related donors and their recipients since 1968. This continues to be performed with care and deliberation. A total of 801 consecutive living donor kidney operations have been performed in the past 21 years. There have been no deaths in the donor patients and none required a return to the operating room for complications in the immediate postoperative course. Two of the donor patients are known to have later developed kidney disease and progressed to chronic dialysis. One of these two patients has received a transplant. It remains our opinion that the excellent early and long-term patient and graft survival in those patients receiving living related donor kidneys, when compared to cadaveric recipients, justifies this form of treatment. Despite this conclusion, the risks of operative death and later illness resulting from or con-



FIG. 5. The donor and recipient leaving the Peter Bent Brigham Hospital after the first successful living related donor operation.

## SUCCESSFUL HOMOTRANSPLANTATION OF THE HUMAN KIDNEY BETWEEN IDENTICAL TWINS

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This report documents the successful transplantation of a human kidney from one identical twin to another. The function of the homograft remains excellent 12 months after the operative procedure. Previous attempts at renal homotransplantation, both clinically and experimentally, have been unsuccessful with one exception. In dizygotic cattle twins, a kidney transplant has survived and functioned for at least nine months. Success in this instance, however, presumably resulted from the production of an acquired mutual tolerance to each other's tissues by the mingling of fraternal protein in the common placental circulation.<sup>1</sup> Transplantation of the kidney in dogs and other animals rarely maintains function for more than a 10-to-14-day period in spite of vigorous attempts to modify the presumed antibody response that results in rejection of the homograft. Similarly, permanent function has not been maintained in a human renal homograft,<sup>2</sup> although in one such instance adequate renal function in a transplanted kidney has persisted for five and a half months.<sup>3</sup> The ultimate cause for rejection in such cases is in all probability differences in individual tissue specificity. Since, however, skin homografts between identical human twins have survived permanently,<sup>4</sup> it might be expected that renal homotransplantation might also be successful when performed between identical twins. The following case history describes such an event.

### REPORT OF A CASE

A 24-year-old, white, single male was apparently in excellent health until 14 months before his first admission to the Peter Bent Brigham Hospital. Except for scarlet fever at age 5 without apparent complications, the history was noncontributory. A few months prior to his discharge from military service, the patient noticed some puffiness about the eyes on awakening in the morning, and on a routine physical examination some elevation of blood pressure was noted. During a five-month study period while at the Boston Public Health Service Hospital, he remained essentially asymptomatic except for epistaxis. Physical

• A patient whose illness had begun with edema and hypertension was found to have suffered extreme atrophy of both kidneys. Because of the steady worsening of the condition and the appearance of uremia with other unfavorable prognostic signs, transplantation of one kidney from the patient's healthy identical twin brother was undertaken.

Preparations included collection of evidence of monozygosity and experimental transplantation of a skin graft from the twin. During the transfer of the healthy kidney it was totally ischemic for 82 minutes. Evidence of functional activity in the transplanted kidney was obtained.

The hypertension persisted until the patient's diseased kidneys were both removed. The homograft has survived for 11 months, and the marked clinical improvement in the patient has included disappearance of the signs of malignant hypertension.

examination was negative except for a consistently elevated blood pressure averaging 170/100 mm. Hg. Pertinent laboratory findings included persistent 2 to 3+ proteinuria. The urinary specific gravity was fixed at 1.010 and microscopic hematuria

From the medical and surgical services of the Peter Bent Brigham Hospital and Harvard Medical School.

This study was supported in part by grants from the John A. Hartford Foundation, Inc.; the Medical Research and Development Board, Office of the Surgeon General, Department of the Army; the U. S. Public Health Service; and the American Heart Association.

The table and figure 1 have been omitted from THE JOURNAL and will be included in the authors' reprints.

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2. Lawler, R. H., and others: Homotransplantation of the Kidney in the Human: Supplemental Report of a Case. *J. A. M. A.* 147: 45 (Sept. 1) 1951. Kiss, R.; Teimurier, J., and Milliez, P.: Quelques essais de greffe de rein chez l'homme. *Mém. Acad. chir.* 77: 755, 1951. Michon, L., and others: Une tentative de transplantation rénale chez l'homme: aspects médicaux et biologiques. *Presse méd.* 61: 1419, 1953.

3. Hume, D. M.; Merrill, J. P.; Miller, B. F., and Thorn, G. W.: Experiences with Renal Homotransplantation in the Human: Report of 9 Cases. *J. Clin. Invest.* 34: 327, 1955.

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FIG. 6. This landmark publication demonstrated, for the first time, that organs could be transplanted between identical twins. This operation lead Merrill and Murray to develop the first successful program of renal transplantation in the United States.

tributed to by such treatment cannot be discounted. Thus the transplant surgeon and the donor must accept the immediate operative risks for the potential long-term gain for the recipient. However, as the results of cadaveric transplantation improve (and they will), this position will change.

Live donor transplantation, regardless of the organ source, is based on informed consent. A careful and detailed discussion of the risks, both known and unknown, the chances of success and failure, and above all, a frank discussion with the donor about the option of using cadaveric organs are absolutely essential. The presentation to the donor must be made by the donor surgeon and not only by the recipient surgeon. The two main reasons for using live donors are better long-term graft survival and the improved elective time of the operation, which thus allows the recipient to avoid the wait for a cadaveric donor, *i.e.*, the problem of organ shortage. The introduction of living donor transplantation other than between identical twins began with the development of azathioprine. Calne and Murray<sup>19</sup> noted that azathioprine was an effective immunosuppressive agent for prolonging survival of canine renal allografts. The drug was then used in the treatment of renal allografts in recipients of nonidentical living related donors and also in the recipients of cadaveric

kidneys<sup>18</sup> (Fig. 7). Starzl<sup>20</sup> (Fig. 8) recognized that graft rejection could be reversed by combining high-dose prednisone with azathioprine (Fig. 9). These two drugs became the cornerstone of renal transplant immunosuppression for the next 15 years. In 1965 and 1966, the human use of heterologous antilymphocyte sera was combined with azathioprine and prednisone by many transplant centers as a means of inducing graft acceptance in the early post-transplantation course. Some years later it was recognized that reversal of allograft rejection could also be achieved with antilymphocyte globulin and a monoclonal antibody. Najarian and colleagues<sup>21</sup> compared the clinical results of cyclosporine to those of antilymphoblast globulin, azathioprine, and prednisone and observed that both groups of patients had equal long-term graft survival. Their experience, as well as others, has further confirmed antilymphoblast globulin as important in the induction phase of immunosuppressive therapy. The introduction of cyclosporin A in renal transplantation in 1983 has had a substantial impact on improving graft survival in patients receiving cadaveric kidneys. This drug has been especially beneficial in prolonging allograft survival in recipients of liver, pancreas, and heart transplants. Each immunosuppressive agent underwent extensive testing in animals, using the canine renal allograft as the model to study the

## Renal Homotransplantation in Man in Modified Recipients \*

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RENAL homotransplantation has been carried out in six patients with terminal renal disease. All the patients had been anuric or severely oliguric for weeks or months prior to transplantation and had been kept alive by chronic dialysis. The immune suppression was accomplished either by supervoltage total body radiation and drugs or by radiation of the spleen and transplanted kidney and drugs. Four of the six patients are still living two weeks to six months after transplantation.

There are several unusual features of these cases, including: 1) bilateral nephrectomy prior to transplantation in three patients for severe hypertension or subacute glomerulonephritis; 2) successfully functioning kidney transplants from donors whose blood types differed from those of the recipients; 3) a functioning transplant which had been iced and stored prior to transplantation; 4) the appearance of an unusual plasma protein during threatened transplant rejection; 5) the use of stained urinary sediment to follow changes in the transplanted kidney; and 6) the management of a patient through two major operations with no urinary function before or for weeks after.

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Although the ultimate success of a renal transplant must be assessed in terms of years, and although these patients do not yet meet these long-term criteria the transplanted kidneys in several instances continue to function well, and a good deal of new data, some of which contravene established transplantation dicta, have been accumulated.

## Methods and Selection of Cases

## Methods of Dialysis

All of the patients in the series required dialysis prior to transplantation. Peritoneal dialysis<sup>4,66</sup> was used in most cases, but some patients were also maintained on hemodialysis,<sup>60</sup> in the early stages by means of a twin-coil kidney<sup>7,63,68</sup> and later with the Kiil kidney.<sup>65</sup> External shunts of the type described by Scribner<sup>121</sup> were used in all patients undergoing hemodialysis. Peritoneal dialysis was used intermittently on some patients, while on others it was used continuously, employing the standard Impersol solution to which varying amounts of potassium and 5.0 mg./L. of heparin were added. One patient was dialyzed continuously for 34 days and another for 21 days. Both patients underwent bilateral nephrectomy during this period. The nephrectomies were accomplished extraperitoneally and dialysis continued without interruption. It was possible to maintain a BUN in the normal range throughout the entire operative period by this technic. Peritoneal dialysis was usually the method of choice because it was simpler, and could be car-

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FIG. 7. The clinical application of azathioprine allowed renal transplantation to be performed in the living related donor and the cadaveric recipient. Combined with prednisone, it became the cornerstone of immunosuppressive therapy.

ability to prevent or reverse rejection. The current immunosuppressive regimens are more complex and involve the sequential use of three or four drugs in the early post-transplantation course, reserving high-dose prednisone and/or monoclonal antibody for the treatment of acute rejection.

During the past 10 years, Sutherland and Najarian<sup>22</sup> (Fig. 10) have developed living related donor pancreas transplantation in a carefully selected group of patients with type I diabetes. This operation requires a donor distal pancreatectomy with pancreatic revascularization using the iliac vessels in the recipient. Although the results have been encouraging, allowing a number of patients to be free of insulin, the risks to the donor appear to be greater than those of a nephrectomy. Quite properly the experience to date in this country has been primarily concentrated in one center. More recently the ethical consider-

ations of performing hepatic transplantation with living donors has been described in which a liver lobe from a parent is transplanted to an infant with advanced liver disease.<sup>23</sup> The technical considerations appear feasible, but again the risks to the donor seem to be substantially greater than with a nephrectomy. Those two techniques of additional organ procurement from living donors serve to emphasize the increasing pressures exerted on the donor and the transplant surgeon, largely because of the short supply of cadaveric organs.

Recently it has been reported from other countries that commercialized living unrelated organ donation has occurred in which the donor is paid by the recipient through a middleman (*i.e.*, broker).<sup>24,25</sup> The sellers, *i.e.*, the donors, are impoverished people from underdeveloped countries who receive little or no medical care after nephrectomy. The federal law in this country makes the sale of organs



FIG. 8. Dr. Thomas E. Starzl, Professor of Surgery at the University of Pittsburgh, has been involved with every aspect of organ transplantation from the early 1960s to the present time. His career has included transplantation of the kidney, liver, pancreas, and intestine. The clinical programs under his direction have been outstanding for more than 25 years.

illegal, and thus these ethical decisions are avoided. Nonetheless the international problem of organ shortage is a fact and the attempt to buy organs will continue to be a problem in those countries where laws permit such practices. The purchase of organs not only further separates the treatment of the poor from the rich but also uses organs from the poor to serve those patients with financial resources.

#### *The Living Unrelated Donor*

A brief and less-accepted venture in 1965 included the use of unrelated living donor kidneys obtained from prisoners.<sup>7</sup> These organs, because they were unrelated, were similar to cadaveric organs from the standpoint of histocompatibility matching and in terms of graft survival. Because of the potential rewards to the donor, including the reduction of prison sentences, the ethical concerns far

outweighed the potential benefits and the procedure was discontinued. More recently, with improved immunosuppression, the question of using unrelated living donors (spouses, cousins, and so on) has been re-examined and excellent graft survival achieved in carefully selected patients.<sup>26</sup> The advantages of using unrelated living donors include early transplantation without waiting for a cadaveric organ and minimization of the risk of preservation injury, thus allowing more aggressive immunosuppressive therapy to prevent rejection in the early post-transplantation course. The negative features are the same as those noted for the living related donor. On balance, it would seem that in select cases unrelated living donors are acceptable candidates for kidney donation.

A repeated question of concern in living related kidney donation is the potential for financial gain by the donor. Outright purchases of organs from relatives have been opposed by the transplant profession, and if known that the donor has arranged a financial deal with the recipient, the decision to proceed with the operation should be discontinued. This matter becomes more complicated if the recipient and his or her family are willing to provide minimal or modest compensation for time lost from work by the donor, either by cash transfer, purchase of groceries, payment of rent, or performing the duties of the donor until he or she recovers and can assume normal life (*i.e.*, farm chores). Although there is a difference between outright organ purchase and compensation for lost revenue from a donor in a family in which financial resources are limited, the gray zone can be broad and ill defined. In some circumstances kidneys have been purchased by recipients with financial means and the organ donor was financially compensated for the organ.

#### *The Cadaver Donor*

Living donor transplantation, as the term implies, requires that a kidney be given to a recipient who is fortunate enough to have a willing friend or relative as a donor. The obvious limitation of securing organs from live donors stimulated the notion that organs and tissue be obtained from cadaveric source. This idea was described in 1947 by Dr. David Hume when he removed a cadaveric kidney and sutured the renal artery and vein to the brachial vessels in a young woman with postpartum renal failure. The kidney functioned as a temporary means of dialysis until she recovered.<sup>27</sup> Hume proceeded to transplant cadaveric kidneys but without success due to rejection until the introduction of azathioprine in 1962. For the next 10 years cadaveric renal transplantation was primarily limited to medical centers located in areas of greater population density where there were large numbers of trauma patients with fatal neurologic injuries. In the mid 1960s, with the increasing use of ventilators, improved endotracheal tubes,

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## THE REVERSAL OF REJECTION IN HUMAN RENAL HOMOGRAFTS WITH SUBSEQUENT DEVELOPMENT OF HOMOGRAFT TOLERANCE

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FIG. 9. Starzl and others recognized that allograft rejection need not be an all-or-none phenomenon and that reversal of rejection by prednisone could lead to long-term graft acceptance. The authors recognized that excessive immunosuppressive therapy could lead to marrow suppression, infection, and death.

BECAUSE OF the high failure rate after renal homotransplantation, there has been an air of pessimism concerning the possibility of long term function of the grafted kidney. The immunologic processes subserving rejection are generally thought to be so powerful and persevering that consistent success cannot be expected with the use of any of the currently available methods of antirejection therapy.

Recent personal experience in caring for patients with renal homografts has resulted in alterations in many of our preconceived notions concerning the management of such patients. It has led to the beliefs that the rejection process can almost never be entirely prevented, but that its effects can be reversed with a high degree of regularity and completeness. Furthermore, the subsequent behavior of patients who have been brought through a successfully treated rejection crisis

suggests the early development of some degree of host-graft adaptation, since the phenomenon of vigorous secondary rejection has been encountered only once.

### METHODS

The material consists of our first 10 patients who received renal homografts from living donors. All recipients were males. The operations were performed between 24 November 1962 and 15 May 1963. The patients have been followed up to 1 July 1963. Excluded from consideration are 2 patients in whom cadaveric kidneys were used as well as a homotransplantation between identical twins, which has been described previously (16). The 10 patients have in common that the homografts were previously normal organs and that injury during transfer was minimized by the provision of cooling during the average ischemic period of 39 minutes. There was one donation from mother to son, and there were 5 from siblings, including 2 pairs of fraternal twins. In the other 4 patients, there was no genetic

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and the development of intensive care units, general surgeons and neurosurgeons were confronted with the long-term management of patients with severe intracranial injuries and absence of spontaneous respiration. At that time there were no available criteria to determine the probability of neurologic recovery and ventilatory support continued until infection intervened and caused the patient's death.

### Brain Death

The decision to accept brain death as synonymous with death of the patient was discussed in 1965 at a Ciba Symposium when Alexandre<sup>28</sup> suggested that organs could be removed from an individual with an intact circulation if there was absolute evidence of brain death. This was established at that time by cerebral angiography confirming

the absence of cerebral blood flow. Soon thereafter the concept of brain death was proposed in the United States, but its acceptance did not come easily and was reviewed in 1968 by Beecher.<sup>29</sup> A definition of irreversible coma, established by the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death, was published in 1968.<sup>30</sup> Beecher provided additional safeguards for the primary physician, indicating the family should be informed and, if there were medicolegal or criminal considerations, the proper authorities should be contacted. He summarized the discussion as follows: 'One can distill from the foregoing two major conclusions. The first is that it is clear beyond question that a time comes when it is no longer appropriate to continue extraordinary means of support for the hopelessly unconscious patient. Pope Pius XII spelled this out. Secondly, a strong case can be made that society can ill afford to discard the tissues

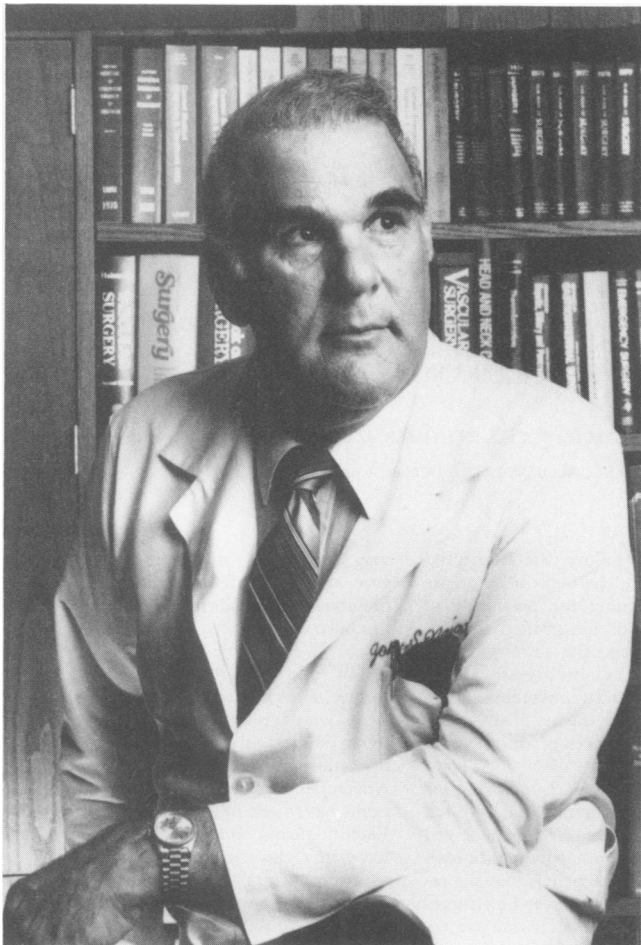


FIG. 10. Dr. John S. Najarian, Professor and Chairman of Surgery at the University of Minnesota, has been active in organ transplantation from 1964 to the present time. His contributions range from experimental studies in rejection, advances in clinical immunosuppression, and transplantation in the diabetic patient. The introduction of segmental pancreas transplantation from living related donors was the first such successful operation for replacement of insulin in the diabetic patient.

and organs of hopelessly unconscious patients so greatly needed for study and experimental trial to help those who can be salvaged. This can come about only with the prior concurrence of those involved, the agreement of society and finally approval in law'.<sup>29</sup> Ten years later acceptance of the death of the brain as death of the patient was reviewed by Black,<sup>31</sup> who noted that 'the entity brain death not be confused with prolonged vegetative existence.' Thus patients with spontaneous breathing or movement associated with severe neurologic impairment do not fulfill the criteria of brain death and are not candidates in whom discontinuation of life support should be considered. Black recognized the 'gray zone' of neurologic injury with respirator dependence but occasional spontaneous efforts at breathing and emphasized that 'to deal with it as brain death is misleading.'

Brain death has become the basis for cadaveric vascular organ procurement. Its recognition and acceptance, when coupled with the Required Request Law,<sup>32</sup> should, by all accounts, have led to increased organ procurement. The Required Request Law states that in the presence of death, the next of kin should be asked by the primary physician if they wish to donate organs from the deceased patient. This law, passed in an effort to increase organ procurement, has not been as helpful as hoped. First the Required Request Law suggests that the increase in the request for organ donation by physicians pronouncing a patient brain dead will result in an increase in organs offered. This assumption is based on the premise that the public is knowledgeable about the need for organs for transplantation and, by understanding this need and accepting brain death, the family will concur with the request for donation. The error in this conclusion lies with the assumption that the public is knowledgeable about the need for organs and agrees with the concept of organ donation. The lack of organ donation is not the result of selfish people but rather a lack of education about the subject, and especially involves those with different social, cultural, and ethnic backgrounds. In general those relatives with a greater level of education are more likely to provide consent for organ donation. The definition and acceptance of brain death remains a pivotal point in organ transplantation in providing a partial solution to the increased need for organs by using scientific progress to resolve the decision to terminate support in those patients with fatal and irreversible neurologic injury.

Many transplant centers (ours included) receive letters from condemned prisoners awaiting electrocution who wish to donate their organs after death. Their request presupposes that their organs would be useful and thus their death be carried out in such a way to preserve their physiologic function. My personal experience has been to decline such offers. However the question could be raised that organ procurement after death would be the same as in other heartbeating cadavers. The obvious need would be to achieve a situation in which the death penalty produced a heartbeating cadaver. The subject is not a pleasant one and I suspect has been avoided largely because of the potential gain that might accrue to the prisoners. It is perhaps fortunate that the actual numbers of organs gained for transplantation by this method would be minimal because the numbers of prisoners executed are few. As noted by Moore,<sup>13</sup> 'there seemed to be an unacceptable social stigma attached to it: profiting from the ultimate punishment.'

### *Organ Preservation*

Organ preservation *per se* is not an ethical problem but does provide a method to preserve organ function after

it has been removed from the body and until a recipient patient can be selected. Because of its importance to organ procurement and cadaveric transplantation, some comments on preservation are appropriate. The development of renal preservation using pulsatile perfusion with hypothermia was first proposed by Dr. Folkert Belzer,<sup>33</sup> in 1967 (Fig. 11). The combination of renal preservation with organ procurement using either brain death or cardiac cessation as a means of determining patient death was the first step toward the development of organized organ procurement and preservation programs (*i.e.*, organ banks). In 1969 Collins et al.<sup>34</sup> published a method of renal preservation using hypothermic cold storage with a hyperkalemic, hyperosmolar solution. These two methods of preservation were the only options until 1989 when Belzer et al.,<sup>35</sup> developed the University of Wisconsin preservation solution that extended the limits of renal preservation to 60 hours and liver and pancreas preservation to more than 24 hours. This immediately diminished certain logistic problems of procurement, organ sharing, and transplantation.

### *Organ and Tissue Banks*

Procurement of organs and tissue for transplantation became a practical reality with the development of organ preservation. The establishment of 'brain death,' combined with organ preservation in the early 1970s, led to the development of clinical organ preservation laboratories. These soon evolved into hospital or transplant center 'organ banks' and then later to regional organ procurement organizations. These organizations not only procure and store organs but also facilitate the selection of the recipient patient, transport organs to other transplant centers, and coordinate the notification of other transplant teams in obtaining extrarenal organs. The organ procurement organization, under the direction of a medical director, usually a transplant surgeon, is supported by paramedical personnel called coordinators. Concomitant with the development of organ procurement for kidney, liver, heart, pancreas, heart-lung, and lung transplantation was the use of human aortic valves for aortic valve replacement, skin for coverage in severely burned patients, and bone for replacement in the resection of bone tumors. Thus the organ bank has evolved into an organ and tissue center requiring careful selection and monitoring of all organs and tissues procured. This includes bacteriologic and serologic testing of tissue and organs, including careful analysis of the medical histories of cadaveric donors to exclude transmissible diseases.

Organ procurement organizations were developed largely by transplant programs through the efforts of transplant surgeons. These programs comply with the ethical concerns of organ distribution following the

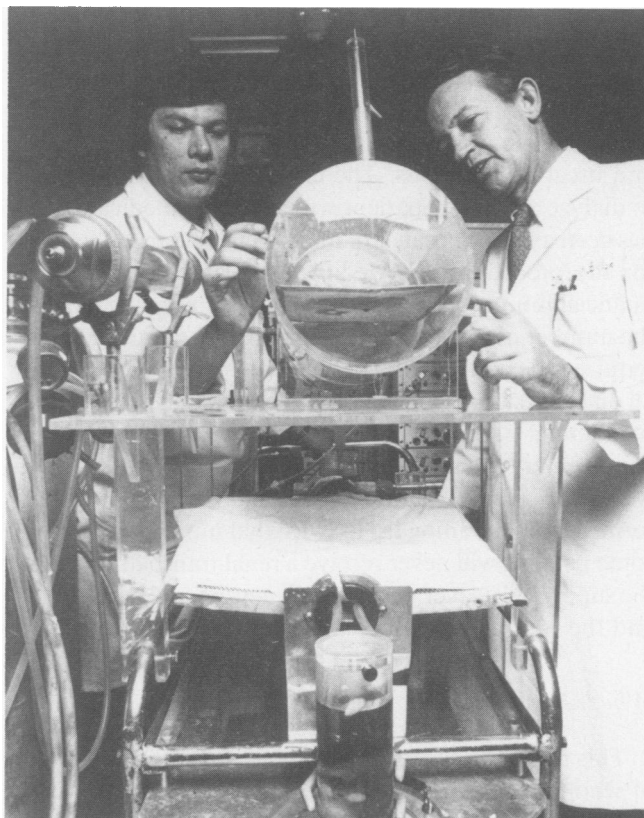


FIG. 11. Dr. Folkert O. Belzer, Professor and Chairman of the Department of Surgery at the University of Wisconsin, is shown above on the right with his original renal preservation machine using pulsatile perfusion. Dr. Belzer has carried out experimental and clinical studies in organ preservation for more than 20 years, culminating in the recent development of the University of Wisconsin (UW) solution. Mr. Bob Hoffman on the left, the first organ procurement technician in this country, continues to pursue the technical and scientific aspects of organ perfusion.

guidelines established by the United Network for Organ Sharing (UNOS), the effector arm of organ procurement. Tissue procurement to the contrary is less well regulated and the guidelines for procurement and processing remain under the control of the individual procurement organization. Tissue procurement programs will require further study and careful planning for the projected growth of the increasing need for tissues and isolated cells for transplantation. The available opportunities to develop 'for profit' companies will further test the ethics of organ and tissue procurement.

### *The Cost and the Demand*

The numbers of patients with renal failure waiting for cadaveric organs was limited until 1972 by the shortage of financial support available for patients requiring dialysis for end-stage renal disease. Government support of patients with end-stage renal disease has allowed all such

patients to be candidates for dialysis or transplantation, without regard to their financial needs. In 1988 more than 114,000 patients were on dialysis, with an estimated total cost of more than \$4.4 billion a year. Obviously the decision to place a patient on dialysis has ethical, medical, and fiscal implications. The ethical decision of whether to dialyze an elderly patient with multiple medical illness has been avoided because of the available financial support for the procedure *via* Medicare. Because there was no financial limit to the number of patients receiving dialysis, the number of these patients expanded, as did the facilities required to cope with the patient care need. Although not all dialysis patients are transplant candidates, the number of potential transplant recipients has expanded far beyond the number of available cadaveric kidneys. In 1988 there were 7217 cadaveric renal transplant operations performed from a waiting list of twice that number. Therefore some patients will never receive a renal transplant because the supply of cadaveric organs will never equal the demand and the waiting list will continue to grow.

#### *Which Patient Receives the Organ*

This raises the complicated and unanswerable question of who deserves a kidney the most and by what means should organs be allocated? In 1984 the National Organ Transplant Act (public law 98-507) was signed by President Reagan. The Organ Procurement and Transplant Network (OPTN) was created, and through the OPTN the United Network for Organ Sharing (UNOS) was awarded a contract to establish a national network for organ procurement and distribution. The UNOS then adopted a point system allowing a fair and equitable distribution of organs to recipient patients. This prevented the allocation of organs to patients through bias of either the transplant surgeon or the referring nephrologist. The question was raised as to how many, if any, organs should be allocated to foreign nationals with end-stage renal disease. Because the number of organ donors are finite, the number of cadaveric transplant operations will be approximately the same number. If organs from United States citizens are given to non-United States patients, then the waiting list for cadaver organs will increase even more. Can or should the United States use its short supply of cadaveric organs for patients outside the United States? If one elects to do so, what is the negative impact on patients in this country? If one considers this a question of ethics, it must also be a question of finance because the cost of dialysis is borne by the United States Government *via* the Medicare program. Still further one needs to ask whether it is 'ethical' to provide organs only to those foreign nationals who have the financial means to come to this country for treatment. These questions are not theoretical and have been the subject of considerable

discussion. Quite simply put, organs are a resource. They cannot be made, cannot be purchased, and must be donated. The shortage of organs has been addressed by the Federal Government through grant support for the development of organ procurement organizations. The Required Request Law (Pub. L. 99-509),<sup>32</sup> enacted by Congress in 1986, went into effect in March 1988 in an effort to make families of patients and the patients themselves aware of the opportunity to donate organs and tissues. This law, as mentioned, has had only modest impact on organ donation. For the past 10 years in Alabama, we have had an extensive network of communication with more than 60 hospitals in the state involving contractual arrangements for organ procurement. In 1988, 650 personal contacts were made by coordinators of the Alabama Organ and Tissue Center about organ donation. The rate of organ donation in Alabama remains about 20 donors per million people (80 to 90 donors per year). Despite strong statewide support for organ donation reinforced by the Required Request Law, the number of kidneys donated in the past 5 years has remained about the same. The reasons for the failure to increase the number of vascular organs is unclear because the number of tissue donors has grown considerably. It is certain, however, that improved techniques of request will be necessary by organ procurement organizations if there is to be an increase in organs donated.<sup>36</sup> The solution to the organ shortage in the near future will be improved only through public education, especially of those individuals between the ages of 18 and 45.<sup>37</sup> Despite these efforts it is likely that the number of available organs will be insufficient for those patients requiring transplantation. Therefore other long-term solutions must be found.

#### *The Xenograft*

One such alternative to organ shortage is the use of xenografts or heterografts. This concept is not new and was reported by Starzl<sup>38</sup> in 1964 and by Reemtsma<sup>39</sup> in 1964. Although the grafts were rejected in 6 months or less, the duration of function of primate kidneys was surprising in view of the limited methods of immunosuppression available. Several years after the use of renal xenografts there were a few unsuccessful attempts to use cardiac xenografts. More recently cardiac xenografts have been used as a bridge to temporarily replace a failing heart until an allograft can be identified.<sup>40</sup> This maneuver clearly makes that patient a high priority for the next available human heart and, as such, will limit the number of organs for the better-risk patient. In this circumstance, who should receive the next organ? The sickest patient with perhaps a lessened chance of survival or the patient in better overall health with a greater chance of survival? The limited number of hearts creates this question.

If one calculates the number of vascular organs required for transplantation for patients with end-stage renal, cardiac, and hepatic disease and diabetes, the likelihood of providing this need seems nearly impossible. It remains uncertain if the organ shortage can be resolved only by improved organ donation and it is possible that the demand will always exceed the supply. If this conclusion is correct, it is probable that the only long-term solution to this logistical problem is the use of xenograft tissues and organs. Although the histocompatibility of humans to subhuman primates has already been tested with the kidney transplants performed in the 1960s, the frequent use of such organs today is not likely. First the public response to the use of organs from subhuman primates would be strongly negative, and second the subhuman primate population would rapidly be destroyed. How does one compare the social value of the apes, chimpanzees, and baboons *versus* that of humans? For these reasons it seems probable that xenograft organs for transplantation should be those removed from animals used for food consumption. This would avoid the ethical questions of using primate organs and place the challenges on overcoming the immunologic barrier of xenograft rejection. Obviously this question can only be answered with a sustained research effort.

#### *Which Patients to Receive Organs*

Which patients should undergo transplantation if organ procurement becomes the rate-limiting factor has not yet been addressed. The patient's age, as well as the primary disease causing the organ failure, would need to be taken into consideration. For example, transplantation of kidneys into patients with long-standing type I diabetes with known coronary artery disease will have a shorter life expectancy in the absence of rejection due to the primary disease of diabetes and its contribution to atherosclerosis. Thus is it proper to exclude such patients from cadaveric transplantation and use organs for younger patients without diabetes who have a longer life expectancy? The practice has been to transplant the patient as the need arises, thus avoiding the question of allocation of limited resources. It is possible that the organ shortage may eventually require physicians and, ultimately, the government to consider using organ transplantation for those patients in whom the primary disease and long-term graft survival is largely limited by rejection and not the patient's primary illness. Some have questioned whether one patient should receive three organs as opposed to three patients receiving one organ each, *i.e.*, save three lives instead of just one life. Equally difficult to answer is how many times should a patient be retransplanted if the first organ fails.<sup>41</sup> There is clear evidence that second and third kidney transplants survive less well than first-time grafts. However repeat

transplants have been successful and most transplant surgeons are willing to proceed with retransplantation.

#### *The Non-brain-dead Donor*

Because of the acute donor shortage in infants, some transplant surgeons have used organs from anencephalic infants.<sup>42-47</sup> These infants often do not meet the current criteria of brain death. At the same time it is accepted that the chances for survival beyond a few weeks is unlikely. The use of organs from the anencephalic infant requires prompt intubation and ventilatory support at birth. This procedure will prolong life and, in time, convert a living infant with a major neurologic deficit to a brain-dead heartbeating cadaver. Consideration of using organs from anencephalic donors who do not meet the criteria for brain death raises the question of euthanasia, a subject that far exceeds the scope of this discussion. Brain death as defined and accepted by physicians today does not extend to patients described by Black<sup>31</sup> to be in the 'gray zone.' The anencephalic child is such a problem, and although one might conclude that such an infant cannot lead 'a useful and meaningful life,' the decision to accept euthanasia in this circumstance could lead to a similar decision in other less well-defined neurologic conditions (Fig. 12). A recent review of anencephalic infants confirms the existence of multiple congenital defects that may make organ transplantation in such circumstances less useful.<sup>46</sup> The subject of euthanasia has little relevance to organ shortage and should not be considered as important in the effort to increase the supply of organs.

#### *Fetal Tissue Transplants*

The final ethical issue to be discussed is the use of fetal tissue for transplantation. The scientific value of fetal tissue has been resolved and the potential clinical application of pancreatic islet cell transplantation in the diabetic patient is currently under investigation. However the source of fetal tissue remains a controversy because procurement will be largely from abortions. It should be clearly understood that the decision for or against abortion should be kept separate from the potential use of such tissue once death has occurred. This point of ethics is of much greater scope than can be covered in this discussion. However it cannot be ignored and a final decision will require more thought and consideration than have been given to date. At present there is substantial resistance to funding fetal tissue research with federal funds, and the current politics of human fetal tissue transplantation provides an unclear path for the future. Annas and Elias<sup>47</sup> summarized the current views of this complicated subject in April 1989. They stated 'Transplantation challenges our ethical precepts, and traditionally ethics have taken a back seat to the temptations and incentives to perform transplanta-

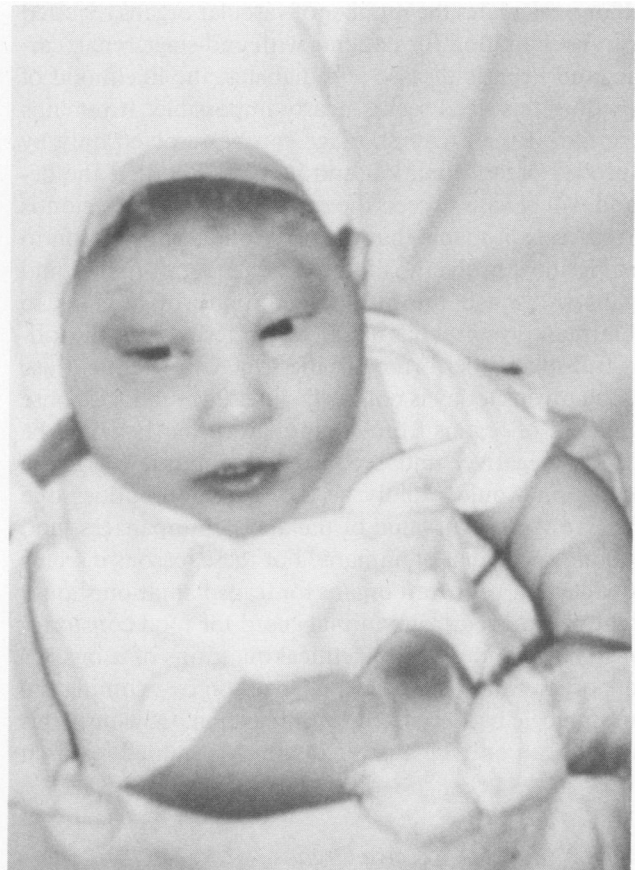


FIG. 12. This infant born with anencephalocoele, as noted on the left, had surgical removal of the extracranial nervous tissue. The infant, an anencephalic, is neither brain dead nor compatible with life. Current criteria do not exist regarding organ procurement.

tions that are the first of a kind. Despite this, the public has generally applauded such transplantation, at least when it is seen as an attempt to save a life that otherwise would certainly have been lost. Transplantation involving fetal tissue is much more problematic, and the public may be less forgiving of ethical shortcuts. Saving a life is usually not at issue, and the source of the tissue, although not illicit, is troublesome to many. The world is watching and this opportunity to demonstrate good science, good ethics and compassionate patient care should not be wasted.'

#### *Transplantation and the Media*

Organ transplantation has occupied public interest for the past 35 years. Cardiac transplantation, first performed in 1966 by Dr. Christian Bernard of Cape Town, South Africa, was an impressive surgical feat that electrified the eyes and ears of the public. At times a carnival-like atmosphere surrounded the subsequent heart transplant operations until a moratorium was achieved due to the problems of graft rejection. Public interest in transplantation accelerated with the introduction of cyclosporin and the major advances in graft acceptance of the liver,

kidney, pancreas, and lung. This scientific progress not only heightened public awareness but also played an important role in the recognition of the shortage of organs. Families plea to the press, radio, and television for organs for their relatives. On occasion the President of the United States became involved on behalf of the patient and the family in their search for an organ. The media has made enormous contributions to transplantation and organ procurement by publishing reports of scientific progress combined with human interest stories. At times, as might be expected, the human interest aspect overshadowed the science and the transplant surgeon was or appeared to be an actor in the play. The 'play' of organ transplantation has been running for more than three decades and in all probability will continue for many more years. Physicians, especially surgeons, will continue to be the actors and often will have little to say about the direction of the play. The ethical conscience of medicine, especially surgery, must accept the major responsibility to be certain that this 'play' does not become a farce. Transplant surgeons and their operations have high public visibility. Although this is not their fault, the transplant community must be careful not to emphasize the science beyond reality. To

do so is to provide the public with false expectations. Those physicians involved in transplantation need to temper their justified enthusiasm and high expectations with appropriate restraint when commenting to the media about new operations and immunosuppressive agents. The media, in turn, must be responsive to these subjects regarding their scientific accuracy and public release. It is not appropriate for us as surgeons to attempt to control the media and its dissemination of information. We should participate with them by providing accurate scientific information presented with realistic expectations using the institution, whenever possible, as the spokesman. The inter-relationship of the surgeon, the media, the pharmaceutical company, and accurate scientific publications will become more important in the years to come. Each member of this group must be careful not to lose the public confidence it now enjoys.

Ethical questions are frequently shunned by surgeons because they are often difficult and have no precise answers. As a result the questions are directed to others and the answers are provided from a nonclinical viewpoint. It is doubtful that this approach will continue to satisfy the public, the press, and eventually the patient. The ethicist has become an increasingly visible member of the field of transplantation and provides a thoughtful and provocative insight into the issues confronting this area of medicine. The answers to the questions are not clear cut and, as such, seem perplexing to those of us who are more comfortable with precise conclusions. The solutions may appear vague because the scientific data is lacking (the anencephalic and organ donation). Difficulty in arriving at well-defined conclusions by surgeons and ethicists should not encourage surgeons to defer the problems to the ethicist. These are clinical questions to be solved by clinicians with consultation by ethicists and others available for advice. Attention to the allocation of resources is unavoidable, and when the resources affect patient care, the physicians and, in this case, the surgeons must participate in those decisions. We really have no choice and should not avoid the challenge.

### Conclusions

Today I have reviewed some of the important ethical questions confronting those involved in the clinical field of organ and tissue transplantation. The problems of the past and present revolve primarily around human experimentation, informed voluntary consent, and the shortage of organs and tissues. It is the shortage of organs that causes the transplant surgeon to consider the living donor. Here the issue of informed consent is of critical concern.

Transplantation of organs requires a donor, and the limited numbers of related donors has long placed an awareness on the cadaver donor. The determination of

brain death by clinical and objective laboratory tests now allow the valid concept of a heartbeating cadaver and the procurement of organs and tissue from the deceased patient under optimal conditions. The development of organ procurement and preservation teams has facilitated the removal and transportation of organs. However the concurrence of donation by the next of kin remains far less than the actual number of potential donors, despite the Required Request Law passed as a means to emphasize the need for organ donation. The solution to this problem will be greater emphasis on public education carefully directed toward schools, colleges, churches, and civic organizations.

The attempt to obtain organs from infants with anencephaly and without confirmed brain death involves the subject of euthanasia, which far exceeds the boundaries of the current guidelines established for fatal neurologic injury. Patients with irreversible neurologic injury but with electrical activity of the cortex are outside the confines of brain death and will require new scientific criteria for organ procurement.

Xenografts are a potential source of organs and tissues that, if successful, would allow us to avoid some of the obstacles limiting organ donation. The use of subhuman primates as organ donors has important limitations in that large colonies of animals are threatened with destruction; these limitations also involve the social concerns regarding animal experimentation. Xenograft tissue and organs from animals used for food consumption, however, might be an acceptable solution if the immunologic barriers causing rejection can be overcome or modified so graft acceptance can be achieved.

The subject of fetal tissue has important implications for using pancreatic islet cells to provide insulin in patients with diabetes mellitus. The decision to use tissue from the aborted fetus has both ethical and political ramifications. The impact on research and its potential clinical applications are such that a reasonable resolution of the problem must be pursued with serious efforts by the public, the medical profession, and the government. The scientific and ethical implications are far more important than to allow discontinuation of fetal tissue research because of the separate and complex subject of abortion. The problem is not the pros and cons of abortion but the use of tissue from a fetus that is no longer alive.

The interface of the media and the transplant profession has been in delicate balance for many years. The transplant surgeon, the media, and the pharmaceutical industry must work closely together to present new scientific data to the public in an accurate and realistic manner. A well-coordinated approach by all three groups is essential if we are to retain public confidence.

In closing I would again like to thank the members of The Southern Surgical Association for the privilege of

serving as your President. It is truly a great honor and one that will remain with me for the rest of my life.

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